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Mg2+ deficient liver cells: At the Cross-road between Inflammation and Dysmetabolism

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A decrease in tissue and serum Mg2+ content has been observed in several endocrinopathies including metabolic syndrome and diabetes. Yet, it has not been elucidated to which extent an altered Mg2+ homeostasis contributes to the onset of these pathologies and/or their complications. Our experimental observation in animals and in liver cells of human origin indicate that Mg2+ deficiency increases G6P entry into the endoplasmic reticulum, and results in an increased oxidation by H6PD. The associated increase in NADPH is then utilized by the 11β-HSD1 to convert inactive cortisone to active cortisol. Consistent with this hypothesis, administration of cortisone to Mg2+ deficient hepatocytes results in a marked production of cortisol, and in the enhanced expression of gluconeogenic genes. In addition, NADPH production support an increased hepatic fatty acid synthesis and intrahepatic triglycerides deposition as attested by the increased expression of fatty acids synthesis-related genes and triglycerides measurement. Furthermore, Mg2+- deficient hepatocytes present decreased insulin responsiveness, which is further compromised by cortisol production. Returning cellular Mg2+ content to physiological levels dramatically decreases cortisol production, and progressively renormalizes expression and activity of H6P, 11β-HSD1, and cortisol-responsive genes. Investigation into the mechanism responsible for 11β-HSD1 increased expression suggest the involvement of increased NFkB translocation to the nucleus and consequently enhanced IL-1β and TNFαexpression in the process. Taken together, our results suggest that Mg2+ deficiency precedes the onset of metabolic syndrome, setting the conditions for an increased intrahepatic production of cortisol and a decreased insulin responsiveness by acting at multiple levels including NFkB translocation, and H6PD and 11β-HSD1 activity and expression while providing a constant entry of G6P into the ER to support the activity of the latter enzymes.

Biography

Andrea Romani obtained his medical degree from the University of Siena, Italy and his PhD from the University of Turin, Italy. Upon completing his postdoctoral studies under Dr. Scarpa, he joined the faculty in the Department of Physiology and Biophysics, Case Western Reserve University, where he is currently Associate Professor. Dr. Romani has published almost 90 peer review articles in high profile journals together with numerous invited reviews and book chapters. He is currently serving as an Editorial Board Member for Archives of Biochemistry and Biophysics, Magnesium Research, World Journal of Gastro-Intestinal Physio-Pathology among others.

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